

## Original article

## Epidemiology of rhinitis in Portugal: evaluation of the intermittent and the persistent types

**Background:** The prevalence of rhinitis is rapidly increasing in recent years and has become a major public health problem in developed countries. A new classification of allergic rhinitis has been proposed by the allergic rhinitis and its impact on asthma group. In this study we aimed to evaluate the prevalence of rhinitis, including different rhinitis subtypes and to describe the severity, rate of diagnosis and use of medication in this pathology.

**Methods:** A cross-sectional, population-based study including 6859 questionnaire responses was performed.

**Results:** The estimated prevalence of rhinitis was 26.1% (48% for intermittent vs 52% for persistent rhinitis). Only about one-third of the rhinitis cases (31.9%) had done skin prick tests (35.3% for persistent rhinitis vs 21.5% for intermittent rhinitis:  $P < 0.001$ ) or had medication prescribed in the last year (34%), (35.6% for persistent rhinitis vs 20.1% for intermittent rhinitis:  $P < 0.001$ ). The prevalence of rhinitis was higher in women (28.2 vs 22.2%;  $P < 0.001$ ). Intermittent/persistent rhinitis showed the following percentages:  $\leq 25$  years (65.6 vs 34.5,  $P = 0.001$ ); 25–65 years (50.2 vs 49.5)  $\geq 65$  years (52.1 vs 47.9). The estimated prevalence of rhino conjunctivitis was 18.4%. In a severity scale from 0 to 10, the mean value was 6.1 points (6.4 for persistent rhinitis vs 4.8 for intermittent rhinitis:  $P < 0.001$ ).

**Conclusion:** A significant prevalence of rhinitis and rhino conjunctivitis was identified in all age groups. The severity, the frequency and duration of the symptoms which classify the persistent type should be considered to establish a more effective treatment and improve the quality of life of the patients with rhinitis.

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Allergic rhinitis (AR) is clinically defined as a symptomatic disorder induced by an IgE-mediated inflammation after exposure to allergens of the nasal mucosa. The symptoms of AR include rhinorrhea, nasal blockage, itching and sneezing which are reversible spontaneously or after treatment. In sensitized individuals, symptoms are triggered by the interaction of the allergen with IgE, which binds to mast cells in the nasal mucosa or to circulating basophils. In contrast, nonAR is characterized by sporadic or persistent nasal symptoms that do not result from immunological events. Diagnosis of AR may be based on the patient's clinical history and supported by results of skin prick tests or radioallergen sorbent tests to detect the presence of allergen-specific IgE in serum (1, 2).

It is not possible to obtain a complete distinction between allergic and nonAR, on the basis of clinical symptoms. The presence or absence of co-morbid conditions is not enough to clarify the rhinitis classification, but may increase the efficiency of the evaluations and the accuracy of diagnosis.

The prevalence of rhinitis has been rapidly increasing in the last few years and has become a major public health problem in developed countries (3, 4). In addition, an increased prevalence of atopic diseases, such as asthma and atopic eczema has been observed (5). Sub-diagnosis is frequent with important impairment in quality of life (1, 6).

Different methodological approaches among studies of epidemiological prevalence can justify some discrepancies observed in populations living in similar geographic areas (7). Self-reported upper and lower respiratory symptoms, through the application of inquiries is often used in large surveys (1, 2). These large surveys using questionnaires do not often distinguish between allergic and nonAR types but give important information about disease prevalence and severity. The information collected can be used later in selected cases to evaluate the occurrence of sensitization.

According to the classic definition rhinitis could be considered as seasonal allergic rhinitis (SAR), also known

as hay fever, and perennial allergic rhinitis (PAR). Described extensively in the epidemiological literature, SAR was associated with outdoor allergens such as pollen and moulds and occurs mainly during the spring season.

Perennial allergic rhinitis was associated with indoor allergens such as dust mites, moulds, cockroaches and animal dander and could occur throughout the year at different seasons. This classification was useful, but considered insufficient (8).

The new classification includes an evaluation of the frequency and duration of the symptoms. Intermittent AR is defined when patients reports having symptoms for <4 days each week or for <4 consecutive weeks. Persistent AR refers to symptoms occurring for more than 4 days a week and for more than four consecutive weeks. Additionally, in the revised classification adopted by allergic rhinitis and its impact on asthma (ARIA), rhinitis can also be divided into 'mild' or 'moderate-severe', according to the severity of the disease which depends on patient self evaluation of symptoms and his/her quality of life (9).

Rhinitis has already been recognized as a significant risk factor for asthma occurrence (10, 11). There are important social and economic costs associated with this disease if impairment of daily activities, quality of sleep and productivity are considered (12).

The aim of this study was to evaluate the prevalence of rhinitis in Portugal, including different rhinitis subtypes applying the clinical criteria of the new ARIA classification. A secondary objective was to describe the characteristics of both the intermittent and the persistent rhinitis groups, including differences or similarities in demography, severity of the symptoms, associated conjunctivitis, self-awareness, rate of diagnosis and use of medication.

## Methodology

The present study was accomplished through the use of 6878 questionnaires applied to volunteers selected from the Medical centres randomized to be as representative of the general population as possible. Selected individuals were invited to participate while they were in waiting rooms. All the individuals, over 16 years of age were included in the study, and had to give their informed consent.

An adherence rate of 85% was obtained. To improve accuracy diagnosis of rhinitis all the individuals that were addressed to the Medical centre for current acute breathing symptoms were excluded in spite of the risk of missing a few cases. In each Medical centre all the questionnaires were filled on a single day.

The data were collected from April 1 to the end of September 2004, during 6 months, avoiding the winter season with its high rate of acute respiratory infections. The questionnaire, based on symptoms or self-awareness

was applied by trained monitors, with previous experience of using this methodology.

Two indicators of rhinitis were considered for the purposes of diagnosis:

A: Doctor -diagnosed rhinitis was defined by a positive answer to the question 'Have you ever been diagnosed as having allergic rhinitis by a doctor?';

B: Information based on symptoms of allergic rhinitis according to positive answer to at least 2 points of the following questions 1 or 2 (Table 1)

The frequency and duration of the symptoms were investigated in order to allocate the patients according to these parameters.

Other questions included in the questionnaire were: ocular pathology assessment, diagnosis and therapeutic procedures characterization (Table 2).

Symptomatic individuals were asked to use a scale from 0 to 10 to classify the severity of their symptoms.

The variables were analysed using descriptive statistics methods: absolute and relative frequency for the categorical variables, and average, median, SD, maximum and minimum for the continuous variables.

Association between the rhinitis prevalence and disease severity and other studied variables was evaluated using a bi-varied analysis of exploratory character.

The chi-square test, *t*-test and the correlation of Pearson were used. The odds-ratio values were also estimated.

All the tests were done considering a level of significance of 0.05.

Table 1. Nasal symptoms

<b>1</b>		
a) Do you usually have problems with sneezing, and an itchy nose?	yes___	No___
b) Do you usually have a blocked nose for more than one whole hour?	yes___	No___
c) Do you usually have a runny nose when you do not have a cold or the flu?	yes___	No___
<b>2</b>		
a) Have you had problems with sneezing, and an itchy nose in the last 12 months?	yes___	No___
b) Have you had a blocked nose for more than one whole hour in the last 12 months?	yes___	No___
c) Have you had a runny nose when you do not have a cold or the flu in the last 12 months?	yes___	No___

Table 2. Clinical information

3. Were nasal symptoms associated with red eyes, itchy eyes and ocular watery?	Sim___	Não___
7. Have you taken drugs for your rhinitis (inhalers or tablets) in the last 12 months?	Sim___	Não___
8 Have your doctor ever asked you to make skin prick tests?	Sim___	Não___

Table 3. Population demography

	Population	Percentage
< 25 years	778	11.4
25-64 years	4413	64.6
> 65 years	1643	24.0
Total	6834	100

## Results

Among the 6878 individuals who completed inquiries 19 were excluded: 16 because they were under 16 years of age and three who did not have permanent residence in Portugal.

Demographic data were analysed for the remaining 6859 individuals.

The sex distribution showed a female predominance (64.6%), with a ratio male/female of 1 : 1.8. The subjects age ranged from 16 to 95 years (Table 3), with an average of 48 year (SD 18).

Doctor diagnosed allergic rhinitis was established in 9.4% of the subjects. Rhinitis prevalence was 26.1% (95% CI 25-27%) based on questionnaire about symptoms as defined in the methodology. The prevalence of rhinitis was higher in women (28.2 vs 22.2%;  $P < 0.001$ ) and similar between different age groups (Table 4).

The nasal symptoms distribution is shown in the Table 5.

The percentages of positive answers to the three points of question 2, about symptoms occurring in the last 12 months, were quite similar to those obtained to question 1 : (a) 32.2%; (b) 23.4% and (c) 21.5%.

Nasal symptoms were presented for more than 4 weeks a year in 67.6% ( $n = 1174$ ) of the cases and for more than 4 days a week in 59.6% of the studied individuals ( $n = 1038$ ). Intermittent rhinitis was diagnosed in 48% of the individuals with nasal symptoms that lasted for

<4 days a week or for <4 weeks a year. Fifty-two per cent had persistent rhinitis, presenting symptoms for more than 4 weeks a year and for more than 4 days a week. The mean age of patients with persistent rhinitis was higher than in patients with intermittent rhinitis (47.2 years vs 49.4 years,  $P = 0.018$ ). Intermittent rhinitis vs persistent rhinitis showed the following percentage values in the three groups considered:  $\leq 25$  years (65.6 vs 34.5,  $P = 0.001$ ); 25-65 years (50.2 vs 49.5,  $P = ns$ )  $\geq 65$  years (52.1 vs 47.9,  $P = ns$ ).

The prevalence of rhinitis in the different regions of Portugal is shown in Fig. 1.

The distribution of persistent/intermittent rhinitis was the following: North: 47.6 vs 52.4%; Centre 48.3 vs 51.7%; Lisbon 49.8 vs 50.2; South-Alentejo: 36.4 vs 63.6%; South-Algarve: 57.1 vs 42.9%. The rhinitis intermittent in Alentejo and the rhinitis persistent in Algarve increased ( $P < 0.05$ ) when compared with the national mean values.

Rural inhabitants presented significantly higher levels of intermittent rhinitis (59.5%) than persistent rhinitis (40.5%) ( $P < 0.05$ ) while urban inhabitants presented similar values for both persistent (50.6%) and intermittent (49.4%) rhinitis.

More than two thirds (70.4%) of the individuals with diagnoses of rhinitis gave a positive answer to the question 'Were nasal symptoms associated with red eyes, itchy eyes and ocular watery?'. The estimated prevalence of rhino conjunctivitis in the Portuguese population was 18.4%. The distribution of ocular pathology among patients with persistent and intermittent rhinitis were similar (52.8% vs 47.2% respectively).

Still considering the new rhinitis classification, we observed that about one third of persistent rhinitis was confirmed by a doctor (34.5%) while medical diagnosis were done only in 14.1% of intermittent rhinitis ( $P < 0.001$ ).

Considering the self evaluation of the severity of disease, using a scale from 0 to 10 points, most of the subjects classify their disease between the levels 4 and 7 (50.3%) with an average value of 6.1 (SD 2.5). About 4% considered their symptoms little annoying (0-1) and 34.5% considered symptoms very severe (8-10) (Table 6).

Patients with persistent rhinitis self reported greater severity of their disease (6.4) than individuals with intermittent rhinitis (4.8) ( $P < 0.001$ ).

The severity attributed to the disease was higher with significant differences in women (Male/Female: 5.64 vs 6.31  $P < 0.001$ ). Ageing did not affect severity ranges.

Skin prick tests were done in 31.9% of the individuals with diagnosis of rhinitis, including 35.3% of persistent rhinitis vs 21.5% of intermittent rhinitis ( $P < 0.001$ ).

Drugs for rhinitis were prescribed to 34.4% of individuals with diagnosis of rhinitis, mainly in persistent rhinitis (35.6%) as it was prescribed only in 20.1% of individuals with intermittent rhinitis ( $P < 0.001$ ).

Table 4. Rhinitis prevalence in different age groups

	Population	Prevalence (percentage)
< 25 years	198	25.6
25-64 years	1149	26.2
$\geq 65$ years	424	25.9

Table 5. Nasal symptoms

	Population	Positive answers (Percentage)
1.		
a) Do you usually have problems with sneezing, and an itchy nose?	2293	33.4
b) Do you usually have a blocked nose for more than one whole hour?	1565	22.8
c) Do you usually have runny nose when you do not have a cold or the flu?	1481	21.6

<b>North</b>	<b>24.6%</b>
<b>Centre</b>	<b>26.7%</b>
<b>Lisbon*</b>	<b>28.7%</b>
<b>South-Alentejo*</b>	<b>30.2%</b>
<b>South-Algarve**</b>	<b>16.0%</b>

\* increased; \*\* decreased ( $P < 0.05$ )



Figure 1. Rhinitis prevalence regional distribution (percentual values).

Table 6. Disease severity self classification

Degrees	Patients	Percentage
0-1	53	3.5
2-3	177	11.7
4-5	480	31.8
6-7	279	18.5
8-10	520	34.5
Total	1509	100

## Discussion

The prevalence of rhinitis, based on two or more positive answers to the questionnaire applied to a sample of 6859 individuals, with ages between 16 and 95 years, was 26.1%.

A positive answer to the question 'Have you ever been diagnosed as having allergic rhinitis by a doctor?' was obtained only in 9.4% of the questionnaires.

This difference emphasizes the sub-diagnosis of this pathology in the Portuguese population. In another SPAIC study carried out in 1998, based on 25 880 questionnaires filled in by general practitioners, a similar low prevalence (10%) was obtained (13, 14). In fact, rhinitis symptoms are often confused with recurrent infectious diseases. Only 32% of the 26.1% of the individuals with rhinitis have already done skin prick tests. Moreover only about 34% of them have taken drugs for this disease, which confirms the lack of information in this issue.

In a previous national epidemiological survey carried out in adults (20-44 years of age) included in the European Community Respiratory Health Survey (ECRHS), which was performed in 1995, the prevalence of rhinitis was 18.9% and 16.7% in the north and central area of Portugal respectively (15, 16). According to the

International Study of Asthma and Allergies in Childhood (ISAAC) conducted in 2002 (Phase III), 24% of the children between 6 and 7 years and 27% of the teenagers (13-14 years) had a diagnosis of rhinitis (17).

Other Portuguese regional population studies confirm the European tendency for increasing prevalence rates and the mean prevalence values are currently above 25% (18). This study was done in individuals from medical centres while waiting for medical care which could contribute to the high number of women who participated in the study. In Portugal all the population are obliged to be registered in medical centres from the national health system and considering the large numbers of individuals included in this study it is accepted that rhinitis affects at least a quarter of the Portuguese population.

It is recognized that seasonal or perennial sneezing, rhinorrhea and congestion of allergic rhinitis affect about 10-30% of adults and 40% of children, making it the sixth most common chronic illness in the United States (19). Over the past 30 years the prevalence of this condition has risen dramatically in industrialized countries. Many of these countries report doubling rates of this disease; which is a trend similar to that seen in other atopic conditions such as asthma (20).

In this study we also included individuals older than 65 years. The rhinitis prevalence found in this elderly group (25.9%) did not differ from the prevalence found in the younger population studied. In fact elderly patients present rhinitis prevalence (for persistent and intermittent types) similar to nonelderly adult patients. More recently some attention has been paid to allergic and respiratory disorders in the elderly. There is some evidence that, even in elderly, allergens can be important triggers of allergic inflammation. Despite the physiological changes in the connective tissue and vasculature that occurs in the

elderly and predispose to chronic rhinitis other triggers such as infections and irritants could also be implicated. Considering the immunological and inflammatory changes associated with the ageing process, rhinitis, which affects about a quarter of individuals in this age group, should not be neglected in diagnostic and therapeutic approaches (21, 22).

With regard to the new ARIA classification, the ratio intermittent/persistent rhinitis was quite similar. These results were different from other epidemiological studies performed in six European countries by Demoly et al. (9). Although this study does not distinguish between allergic and nonallergic rhinitis types it should be stressed that the most frequent sensitization source in Portugal is house dust and storage mites. Indoor allergens are continuous triggers, usually associated with persistent respiratory complaints. A further reason for this observation can be the geographical position of the country in the southern of Europe. In fact, there are several sensitization patterns throughout Europe. Genetics factors, climate, geography, local flora (with changes related to forest fires, agricultural methods, importation of non-native species), pollution and demography are responsible for these different sensitization patterns (23–25). The climate of Portugal changed in recent years and now there is warmer weather with increasingly long springs, summers and autumns. Pollen grains can be counted throughout nearly all the year according to the European Pollen Information Network which integrates the national aerobiology networks (26). The southern regions of the country presented the greatest difference in the prevalence values of rhinitis (30.2% in the Alentejo and 16.0% in the Algarve). The Alentejo is an inland region of Portugal where the incidence of pollen counts reaches very high levels in some warmer days, while the Algarve is on the coast, with a mild weather. In the Alentejo intermittent rhinitis was present in the majority of the patients (63.6%) and in the south coast of Algarve 57.1% had persistent rhinitis.

Also rural inhabitants presented significantly higher levels of intermittent rhinitis (59.5%). The pollen sensitization is higher in urban rather than in rural ones (27, 28). Several factors, such as pollution, particularly vehicle emissions and the increased concentration of ozone in the air can contribute to a continuous symptomatic state of patients with rhinitis (27, 29).

Most of the patients classified the severity of their disease with a medium value of 6.1. The women attributed a significantly higher severity of disease when compared with men, but age did not influence this evaluation. In addition, according to the patients' self evaluation a close relationship was established between disease severity and persistent rhinitis, as expected.

The low rate of diagnostic tests (skin prick tests done in 31.9%) and reduced therapeutic approach (34.4%) may reflect the restricted accessibility to differentiated care in the national health system. Diagnosis and therapeutic procedures were more effective in patients with persistent rhinitis (skin prick tests: 35.3%; medicated: 35.3%). This probably also reflects the higher discomfort felt by these individuals.

It is recognized that symptom under evaluation is common among patients with nasal pathology. The symptoms of allergic rhinitis can lead to headache, irritability, loss of sleep and fatigue, which interfere with cognitive tasks and cause work absences. Families with low socio-economic status tend to ignore some of these clinical manifestations, except if they become persistent and severe.

Several studies in Western countries tested the effect of treatment in AR and confirmed the effectiveness of long-term therapy in quality of life and a decrease in disease burden

Conjunctivitis was present in 70.4% of the patients with rhinitis. Other clinical associations often reported with rhinitis such as asthma were not investigated in the present study and should be evaluated later.

A better knowledge of the impact of rhinitis supported by suitable diagnostic studies, such as specific IgE determinations, can reverse the increasing prevalence observed in developed countries. The severity, the frequency and duration of the symptoms should be considered to establish a more effective treatment and improve the quality of life of the patients with rhinitis.

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## References

- Bousquet J, Van Cauwenberge P, Khaltaev N: ARIA Workshop Group. World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; **108**(Suppl.):147–334.
- Weir E: The burden of rhinitis: nothing to sniff at JMAC. *CMAJ* 2003; **169**:694.
- Devenny A, Wassall H, Ninan T, Omran M, Daud Khan S, Russell G: Respiratory symptoms and atopy in children in Aberdeen: questionnaire studies of a defined school population repeated over 35 years. *BMJ* 2004; **329**:489–490.
- Anderson H, Ruggles R, Strachan D et al: Trends in prevalence of symptoms of asthma, hay fever, and eczema in 12–14 year olds in the British Isles, 1995–2002: questionnaire survey. *BMJ* 2004; **328**:1052–1053.

5. ISAAC Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;**351**:1225-1232.
6. Storms W. Rethinking our approach to allergic rhinitis management. *Ann Allergy Asthma Immunol* 2002;**4** (Suppl. 1):30-35.
7. Crane J, Mallol J, Beasley R, Stewart A, Asher M. On behalf of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase I study group. Agreement between written and video questions for comparing asthma symptoms in ISAAC. *Eur Respir J* 2003;**21**:455-461.
8. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy* 2005;**60**:350-353.
9. Demoly P, Allaert A, Lecaesle M et al. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). *Allergy* 2003;**58**:672-675.
10. Leynaert B, Bousquet J, Neukirch C et al. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;**104**:301-304.
11. Plácido M, Gaspar A, Morais-Almeida M, Romeira A, Almeida-Vau T, Neto-Braga C et al. Rhinitis as a risk factor for persistence of symptoms in childhood recurrent wheezing: an 8-year prospective study. In: Marone G, editor. *Clinical Immunology and Allergy in Medicine*. Naples: JGC Editions, 2003: 437-441.
12. Crystal-Peters J, Crown W, Goetzel R, Schutt D. The cost of productivity losses associated with allergic rhinitis. *Am J Manage Care* 2000;**6**:373-378.
13. Castel Branco MG, Rodrigues J, Ferraz de Oliveira J et al. A cross-sectional epidemiological study of the prevalence of rhinitis in Portugal in the year 1998. *Allergy* 2000;**55**(Suppl.63):39.
14. Loureiro AC, Todo Bom A, Pereira C et al. Prescriptions given by general practitioners to patients with rhinitis. *Allergy* 2000;**55**:43.
15. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;**9**:687-695.
16. Loureiro AC, Chieira C, Pereira AC et al. Estudos epidemiológicos da Asma Brônquica numa população adulta. *Rev Port Imunoalergol* 1996;**4**:35-54.
17. Nunes C, Ladeira S, Rosado Pinto JE. Definição, Epidemiologia e classificação da asma na criança in *A Criança Asmática no Mundo da Alergia*. Rosado Pinto JEMorais de Almeida M, editors. *Euromédica* 2003;35-55.
18. Robertson C, Roberts M, Kappers J. Asthma prevalence in Melbourne schoolchildren: have we reached the peak? *Med J Aust* 2004;**180**:273-276.
19. Agency for Healthcare Research and Quality. [http://www.ahrq.gov/Management of allergic and nonallergic rhinitis \[Evidence Report/Technology Assessment no 54\]](http://www.ahrq.gov/Management%20of%20allergic%20and%20nonallergic%20rhinitis%20[Evidence%20Report/Technology%20Assessment%20no%2054].). Washington: The Agency, 2002.
20. Fernández-Mayoralas M, Caballero J, Álvarez L. Asociación entre dermatitis atópica, rinitis alérgica y asma en escolares de 13 y 14 años. *Anal de Pediatría* 2004;**60**:236-242.
21. Vignola AM, Scichilone N, Bousquet J, Bonisgnore G, Bellia V. Aging and asthma: pathophysiological mechanisms. *Allergy* 2003;**58**:165-175.
22. Huss K, Naumann PL, Mason PJ et al. Asthma severity, atopic status, allergen exposure, and quality of life in elderly persons. *Ann Allergy Asthma Immunol* 2001;**86**:524-530.
23. D'Amato G, Spiekma F, Liccardi G et al. EAACI position paper: pollen-related allergy in Europe. *Allergy* 1998;**53**:567-578.
24. D'Amato G, Liccardi G. Pollen-related allergy in the European Mediterranean area. *Clin Exp Allergy* 1994;**24**:210-219.
25. von Mutius E. The environmental predictors of allergic disease. *J Allergy Clin Immunol* 2000;**105**:9-19.
26. <http://www.rpaerobiologia.com> and <http://www.pollenwarndienst.at>; accessed 2 June 2007.
27. Devalia J, Ruzsnaek C, Davies R. Allergen/irritant interaction – its role in sensitisation and allergic disease. *Allergy* 1998;**53**:335-345.
28. Loureiro G, Rabaça MA, Blanco B, Andrade S, Chieira C, Pereira C. Urban versus rural environment- any differences in aeroallergens sensitization in allergic population of Cova da Beira, Portugal? *Allergy Immunol (Paris)* 2005;**37**:187-193.
29. D'Amato G, Liccardi G, D'Amato M, Cazzola M. The role of outdoor air pollution and climatic changes on the rising trends in respiratory allergy. *Respire Med* 2001;**95**:606-611.